Original Article

COVID-19 infection following influenza vaccine injection and its complications among nurses working in educational-medical hospitals of Ardabil in 2020

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Abstract

Objectives: Health care workers are one of the groups at risk of influenza. Currently, influenza vaccination is very important more than ever before. Influenza is evolutionarily similar to SARS-CoV-2, and they have some common epitopes and mechanisms. Thus reducing the severity of COVID-19 disease by influenza vaccination seems possible. Therefore, the aim of this study is to investigate the relationship between influenza vaccination and COVID-19 infection among clinical nurses. **Methodology:** The present study is a prospective analysis of nurses working in educational-medical hospitals of Ardabil. In this study, two groups of nurses were considered as case and control groups. The collected data were analyzed using SPSS software and descriptive (mean, standard deviation and frequency) and analytical (Chi-square) tests. **Results:** A total of 279 individuals were included in the study according to the research criteria. The maximum duration of the disease was one week in the control group and four weeks in the case group. Chi-square test showed that there was a significant difference in terms of disease duration between the two groups ($P = 0.000$). Chi-square test showed that there was a statistically significant difference in terms of disease treatment between the two groups ($P = 0.000$). **Conclusion:** Influenza vaccine reduces the incidence of COVID-19 and reduces the need for hospitalization in patients with this disease. However, due to the positive effects of influenza vaccine on COVID-19 and its low cost, it is recommended to inject influenza vaccine more than before.

Keywords: COVID-19 disease, influenza, influenza vaccine, nurses

Introduction

Influenza is an RNA virus of the orthomyxoviridae family[1] that includes three strains of influenza virus called A, B, and C[2] that cause acute respiratory infections.[3] Annual influenza epidemics generally occur during the cold seasons of the year due to genetic variations of different strains of influenza virus that are slightly different from previous variants.[4] The majority of seasonal influenza viral loads are associated with two viruses, A and B. Although virus C can also cause disease, the disease is less severe. Outbreaks of influenza B increase only the number of hospitalizations, whereas influenza A, which originates from pigs and birds, increases both the number of hospitalizations and the mortality rate. Compatibility of influenza A virus with humans has led to its worldwide spread. The disease has caused outbreaks of Spanish influenza (1918) and swine flu (2009) in the past.[5,6] Seasonal influenza affects people of all ages,[7] and its

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clinical symptoms generally include myalgia, headache, fever, and cough,[8] which treats over a period of three to five days, although the cough may last up to two weeks.[9] The risk of serious illness and complications from influenza, including lower respiratory tract infection, hospitalization, and death, depends on factors such as old age, cardiovascular, lung, renal, liver, blood disease, diabetes, etc.[7] Influenza is responsible for 3–5 million cases of severe disease and 500 to 250,000 deaths annually.[7] Vaccination is the most effective way to prevent influenza and its severe complications.[10] The European Commission and many other institutions around the world recommend influenza vaccination for people at risk of influenza and its serious complications, especially health care professionals.[11] In addition to the fact that health care workers are one of the groups at risk of influenza, these people can be an important source of infection for vulnerable patients hospitalized for flu. Therefore, achieving a high level of vaccination among health care workers is very important to prevent an increase in the number of patients and reduce the workload of national health systems. Different rates of influenza vaccination are reported each year, depending on government regulations as well as their knowledge and understanding of the disease.[12-14] Influenza vaccination is very important currently than ever before because of the COVID--19 pandemic, which started in late December 2019 with the new variant of coronavirus-2019 (SARS-CoV-2) from Wuhan, China, that is still widespread and active worldwide.[15,16]

Coronavirus is one of the main pathogens that targets the human respiratory system and has previously caused acute respiratory syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV).[17] One of the most important issues regarding COVID-19 is its high prevalence. The coronavirus is transmitted through respiratory droplets of an infected person generated by coughing, sneezing, and talking, and it has infected millions of people around the world.[18,19]

COVID-19 is characterized by a variety of symptoms, from asymptomatic to moderate and severe and death. The patient may initially complain of nausea or vomiting. Fever (not in all cases), dry cough, sore throat, shortness of breath, headache, lethargy, muscle aches, fatigue, normal or decreased leukocyte count, diarrhea, abdominal pain, abnormalities in chest computed tomography as well as complications including injury to vital organs such as lung, heart, liver, kidney, central nervous system and coagulation disorders have been observed in patients infected with the new coronavirus.[20-23]

Treatment for mild cases includes antibiotics, antipyretics, vitamins, and minerals, while in case of respiratory distress, oxygen therapy should be performed according to each person's condition with or without mechanical ventilation.[24]

Given that co-infection with influenza and COVID-19 is associated with an increase in mortality, and also given that reducing the incidence of chronic respiratory diseases reduces the morbidity and mortality of COVID-19, the following hypothesis arises. Influenza-immunized people will show a lower rate of respiratory complications from influenza and therefore better health conditions for fighting against SARS-CoV-2.[14,25] Although influenza vaccine doesn't provide 100% protection, it protects many people from severe complications and mortality, especially the medically vulnerable, thereby reducing the burden on national health systems[14].

As influenza is evolutionarily similar to SARS-CoV-2 and both of them have some common epitopes and mechanisms, reducing the severity of COVID-19 disease by influenza vaccination seems possible and this can also be a step toward reducing the burden on the health system in society.[26] Due to the small number of studies and information in this regard, this study was conducted to investigate the relationship between influenza vaccination and COVID-19 infection among clinical nurses to obtain evidence regarding the effect of the influenza vaccine on the infection of COVID-19 and its complications in order to reduce the burden on the primary health care system.

Methodology

The present study is a prospective analysis of nurses working in educational-medical hospitals of Ardabil. In this study, two groups of nurses were considered as case and control groups. The case group included all nurses working in Ardabil hospitals who had received the flu vaccine in September or October, and the control group included the same number of individuals as the case group and randomly selected nurses working in the mentioned hospitals who did not receive the vaccine. Inclusion criteria included having at least six months of clinical experience before receiving the influenza vaccine, and exclusion criteria were: acute disease during the study (excluding COVID-19), having less than six months of work experience after receiving the vaccine at the clinic, and receiving COVID-19 vaccine during the study. The data collection tool in this study was a three-part questionnaire. The first part included the demographic information of nurses, the second part included a checklist of questions about influenza vaccine injection and its complications, and the third part was related to COVID-19 infection and its complications. Questionnaires related to demographic information and influenza vaccine injection were provided online for the case group nurses. Six months after completing the first questionnaire, questionnaires related to COVID-19 and its complications were sent to both groups and the completed questionnaires were collected. Questionnaires for each group and each person were coded. The collected data were analyzed using SPSS Version 22 and using descriptive (mean, standard deviation, and frequency) and analytical (Chi-square) tests.

Findings

A total of 279 people were included in the study according to the research criteria, of which 139 individuals (49.82%) were in the control group and 140 individuals (50.17%) were in the case group. The average age of the control group was 35.14 years and the majority of them were (124 individuals, 89.2%) women. The average age in the case group was 33.57 years and the majority of them were (119 individuals, 85%) women. There was no

statistically significant difference between the demographic variables of the two groups ($P > 0.05$) [Table 1].

In the case group, 30 (21.4%) nurses were vaccinated with Korean influenza vaccine, 22 (15.7%) with French vaccine, 9 (6.4%) with Indian vaccine, 49 (0 35%) with the vaccines of the Netherlands, and 12 people (86.6%) were vaccinated with Russian vaccine. Also, 17 people (12.9%) did not report this case.

Thirteen nurses had cold symptoms while receiving the vaccine. Five nurses did not answer this question and 122 individuals did not have cold symptoms while receiving the vaccine. Evaluation of complications of influenza vaccine injection showed that the most common complications were related to injection site pain in 69 patients (49.3%), weakness and fatigue in 42 patients (30%), muscle pain in 36 patients (25.7%) and the lowest complication was related to facial swelling and skin rash in 1 person for each of them (0.7%) [Table 2].

During the six months after influenza vaccination, 25 (17.9%) individuals in the case group and 75 (75%) individuals in the control group who did not receive the flu vaccine became infected with COVID-19 during the same period. This number was statistically significant ($P = 0.001$) [Table 3].

Evaluation of the clinical signs of COVID-19 showed that in the group that did not receive the flu vaccine, all patients (100%) had fever, and the most common symptoms in this group after fever included sore throat in 64 patients (3 85%), muscle pain in 54 patients (71.1%) and shortness of breath in 40 patients (52.6%). In the group that received the flu vaccine and was infected with COVID-19, muscle pain in 22 patients (88%), headache in 18 patients (72%), chills and sore throat in 15 patients (60%) and fever in 13 patients (52%) were reported. The study of statistical results showed that there was a statistically significant difference between some common symptoms of COVID-19 in the two groups ($P < 0.05$) [Table 3].

The maximum duration of the disease was one week in the control group and four weeks in the case group. In the control group, 59 individuals (77.6%) recovered in less than one week, but in the case group, the majority of nurses (11 individuals, 44%) experienced a disease duration of two weeks, and none

Table 1: Demographical characteristics and statistical relationship between case and control group

Variable	Case N (%)	Report N (%)	*P* value
Sex			
Male	21 (15)	15 (10.8)	0.29
Female	119 (85)	124 (97.2)	
Age			
20-29	44 (31.4)	27 (19.4)	0.15
30-39	66 (47.1)	77 (55.4)	
40-49	29 (20.7)	34 (24.5)	
50-59	1 (0.7)	1 (0.7)	
Blood type			
A +	46 (32.9)	44 (31.7)	0.79
A -	5 (3.6)	5 (3.6)	
B +	21 (15)	21 (15.1)	
B -	2 (1.4)	1 (0.7)	
AB +	11 (7.9)	16 (11.5)	
AB -	1 (0.7)	0 (0)	
O +	52 (37.1)	47 (33.8)	
O -	2 (1.4)	5 (3.6)	
Allergy			
Yes	19 (13.6)	19 (13.7)	0.981
No	121 (86.4)	120 (86.3)	
Anemia			
Yes	20 (14.3)	27 (19.4)	0.25
No	110 (78.6)	107 (77)	
Vit D deficiency			
Yes	38 (27.1)	53 (38.1)	0.146
No	63 (45)	54 (38.8)	
Not checked	39 (27.9)	32 (23)	
Self-protect			
Yes	129 (92.1)	130 (93.5)	
No	11 (7.9)	9 (6.5)	
Immonobooster drug			
Yes	26 (18.1)	22 (15.5)	0.54
No	114 (81.4)	117 (84.2)	
Immunosuppressant drug			
Yes	7 (5)	6 (4.3)	0.78
No	133 (95)	113 (95.7)	
Immunological disease			
Yes	5 (3.6)	6 (4.3)	0.74
No	135 (96.4)	133 (95.7)	
Underlying diseases			
Yes	20 (14.3)	14 (10.1)	0.28
No	120 (85.7)	125 (89.9)	

Table 2: Influenza vaccination side effects in control group

Variable	Category	*n* (%)
Side effects of the vaccine	Cold symptoms	32 (22.9)
	Injection site pain	69 (49.3)
	Injection site red	21 (15)
	Weakness and fatigue	42 (30)
	Muscular pain	36 (25.7)
	Fever	11 (7.9)
	Chills	8 (5.7)
	Nasal drip	11 (7.9)
	Headache	18 (12.9)
	Cough	4 (2.9)
	Diarrhea	4 (2.9)
	stomach ache	3 (2.1)
	Wheal	2 (1.4)
	Rash	1 (0.7)
	Hoarseness	6 (4.3)
	Shortness of breath	2 (1.4)
	Heart palpitations	5 (3.6)
	Face Swelling	1 (0.7)
	Guillain-Barré syndrome	0 (0)
	Anaphylactic shock	1 (0.7)
	Others	4 (2.9)

of the nurses in the case group recovered in less than one week. Chi-square test showed that there was a statistically significant difference in terms of disease duration between the two groups ($P = 0.000$) [Table 4].

Chi-square test showed that there was a statistically significant difference in terms of disease treatment between the two groups ($P = 0.000$) [Table 4].

Discussion

The aim of this study was to investigate the differences between the incidence of COVID-19 and the complications of the disease in two groups of nurses working in the hospitals of Ardabil province. Nurses working in hospital wards are more at risk of infection with the two respiratory viruses of influenza and SARS-CoV-2 due to direct contact with patients. Simultaneous infection can increase the severity of COVID-19 disease in nurses and thus increase the pressure on the health care system of countries. On the other hand, since nurses are in direct contact with patients, if they are infected with any of these viruses, they can transmit the virus to patients who have an underlying disease and they can experience severe illness and even death.

Table 3: COVID-19 symptoms between case and control groups

Variable	Category	Case *n* (%)	Report *n* (%)	*P*
COVID-19 infection	Yes	25 (17.9)	75 (54)	0.001
	No	115 (82.1)	64 (46)	
COVID-19 symptoms	Fever	13 (52)	76 (100)	0.000
	Sore throat	15 (60)	64 (85/3)	0.007
	cough	2 (8)	32 (42.1)	0.002
	Sputum cough	9 (36)	26 (34.2)	0.870
	Decreased taste	11 (44)	35 (47.4)	0.858
	Decreased smell	12 (48)	36 (47.4)	0.956
	Shortness of breath	10 (40)	40 (52.6)	0.273
	Headache	18 (72)	34 (44.7)	0.018
	Muscular pain	22 (88)	54 (71.1)	0.089
	Chills	15 (60)	37 (48.7)	0.326
	Nausea	10 (40)	2 (2.6)	0.000
	Vomiting	7 (28)	15 (19.7)	0.385
	Diarrhea	9 (36)	7 (9.2)	0.000
	Decreased appetite	19 (76)	21 (27.6)	0.000

Table 4: COVID-19 period and treatment methods between case and control groups

Variable	Category	Case *n* (%)	Report *n* (%)	*P*
Duration of the disease	< 1 week	0 (0)	59 (77.6)	0.000
	1 week	7 (28)	17 (22.4)	
	2 week	11 (44)	0 (0)	
	3 week	6 (24)	0 (0)	
	4 week	1 (4)	0 (0)	
Treatment method	Hospitalization	2 (8)	45 (59.2)	0.000
	Home treatment	22 (88)	20 (26.3)	
	Other	1 (4)	11 (14.5)	

In this study, we selected two groups of nurses working in hospital wards (except Corona ward) in Ardabil province, so that the case group received the flu vaccine but the nurses in the control group did not receive the flu vaccine. Both the vaccinated and unvaccinated groups were almost similar in terms of demographic characteristics, including sex, age, blood type, allergies, anemia, vitamin D deficiency, use of booster drugs as well as immunosuppressive drugs, observance of health protocols (use of mask, Gun, face shield and gloves), history of immunological disease, and other underlying diseases.

The incidence of COVID-19 during the six months after influenza vaccination was two times lower in the group that received the influenza vaccine than in the group that did not receive the influenza vaccine. This finding was consistent with the results of a study by Candelli *et al.*[27] entitled "The effect of influenza vaccine on COVID-19 mortality: A retrospective study". Another study by Zein *et al.*,[28] entitled "Immunization of influenza vaccine during COVID-19," found a similar finding and according to the results the possibility of positive test of SARS_CoV_2 was less likely in vaccinated individuals. This occurs when the vaccine can stimulate a proper innate immune memory so that when other respiratory pathogens such as SARS-CoV-2 enter the respiratory system, the local lung immune system can respond rapidly to the pathogen and prevent the incidence of SARS-CoV-2 and COVID-19.[29] Since influenza is evolutionarily similar to SARS-CoV-2 and the two viruses have some common epitopes and mechanisms, this effect is predictable for influenza vaccine.[26] In a study conducted by Amr Shaaban Hanafy *et al.*[30] on the potential effect of combined influenza and pneumococcal vaccines on the severity of respiratory disease in COVID-19 infection in type 2 diabetic patients, they found that influenza vaccination in diabetic patients by direct stimulation of Toll-like receptor (TLR), stimulating the response of humoral and T cells, producing specific natural killer cells, with enhanced long-term memory, and enabling OX40 and OX40L activation, provides extensive protection against SARS-CoV-2.[30] Also, the lower susceptibility of children to infect with COVID-19 can be strong evidence of the development of nonspecific immunity by vaccines against infectious agents.[27]

Comparing the hospitalization rate in the two groups shows a statistically significant difference, so that the hospitalization rate in the case group was much lower than the control group and most patients with COVID-19 in the case group recovered from the disease at home. Our findings in this study showed that the subjects in the case group had lower disease severity. The lower severity of the disease in the case group can be justified by improved intrinsic and specific immunity, and influenza vaccine by stimulating TLR7 receptors on the surface of dendritic cells, macrophages, and neutrophils produces a faster response through nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB) to a new viral infection.[31] A similar study by Eldanasory *et al.*[32] entitled, "Can the influenza vaccine change the clinical course of COVID-19?" on 92664 patients suffering from COVID-19 showed that among the vaccinated population,

the probability of transferring these patients to the ICU was 8% lower, 18% less likely to require mechanical ventilation than other patients, and 17% less likely to die.[32] In an extensive study in Brazil, after classifying information based on age, sex, and underlying diseases, the protective effect of influenza vaccination on disease severity was determined. They assessed the severity of the disease according to the patient's need for hospitalization in ICU as well as respiratory support and mortality.[27]

A comparison of the disease duration in the two groups showed that the duration of the disease in the case group was longer than the control group. In the case group, the maximum duration of the disease was reported as one week, while in the control group it was four weeks. The study by Shosha *et al.*[33] showed that the length of hospitalization in the vaccinated group is 3-10 days and in the non-vaccinated group is 21-2 days. Although this study is consistent with our study in terms of reducing the severity of the disease in the case group, it is inconsistent in terms of the duration of the disease with our results in this study. According to another study, people who were vaccinated against the flu had a longer hospital stay than those who were not vaccinated. No significant difference was observed between vaccinated and unvaccinated individuals during the time of hospitalization in ICU.[27] This result is consistent with the result of our study; that is, reducing the duration of disease in the case group.

Our study showed that influenza vaccination was effective in hospitalization rate as a result of COVID-19, so that the hospitalization rate in the control group was higher than the case group. Other studies have shown no effect of influenza vaccine on the likelihood of hospitalization, ICU transfer, and death.[29,34] According to these results, this needs more studies with similar samples under the same conditions.

According to the results obtained from the present study, and its effect on reducing the rate of infection with COVID-19 and reducing the hospitalization rate and length of hospitalization caused by it, family physicians can prescribe the influenza vaccine for the people in society, especially vulnerable people. For the elderly and patients with chronic problems such as chronic obstructive pulmonary diseases and diabetics, it can be a step toward reducing the burden on the primary health care system.

Regarding the complications of COVID-19 in both case and control groups, our study showed that the flu vaccine had a decreasing effect on some of the symptoms of COVID-19 and an increasing effect on others. In the meantime, it had no effect on symptoms such as sputum cough, decreased taste, shortness of breath, chills, and vomiting, and these symptoms were almost the same in the case and control groups. Influenza vaccination increased symptoms such as loss of appetite, diarrhea, nausea, muscle aches, and headache after COVID-19 infection, but fever, sore throat, and dry cough after COVID-19 infection were lower in the case group than in the control group.

Conclusion

The flu vaccine reduces the incidence of COVID-19 and the need for hospitalization in people with the disease. Although the duration of the disease may be longer, in vaccinated people, the severity of disease is less than in non-vaccinated people. Influenza vaccination has variable effects on the clinical symptoms of COVID-19, and it is recommended that more detailed studies be conducted to determine the cause. However, due to the positive effects of influenza vaccine on COVID-19 disease and its low cost, it is recommended to inject influenza vaccine more than before.

Key messages

Influenza vaccine administration reduces the rate of infection with COVID-19 and the rate of hospitalization caused by it.

The managers of the primary health care system can consider this result in the planning of the health care system, especially in the case of nurses who are at the bedside, and emphasize this issue.

Considering that family physicians are the first point of contact with people, they can consider this issue and recommend the injection of influenza vaccine during the outbreak of COVID-19, especially in the case of elderly people and those with chronic diseases who are more vulnerable.

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Conflicts of interest

There are no conflicts of interest.

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